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REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The amendments to the claims and new claims 23-44 point out more particularly and claim more distinctly the subject matter of Applicants' invention. No prohibited new matter has been introduced by this Amendment. Applicants reserve the right to pursue in a division or continuation application any subject matter canceled by way of this Amendment without prejudice or disclaimer.

The claims have been amended to remove language which creates alternative steps for the claimed methods and to clarify the claims. New claims have been introduced herein which claim the alternative subject matter amended from the as-filed claims. The following table indicates the basis for each new claim.

New Claim reciting former alternative step	Basis found in claim as-filed
23	7
24	1
25	2
26	3
27	4
28	5
29	6
30	7
31	8

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32	9
33	10
34	11
35	13
36	14
37	15
38	16
39	17
40	18
41	19
42	20
43	21
44	22

Thus, this amendment does not introduce any new matter, is merely corrects an informalities and renders the subject matter of the claims more clear.

I. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-22 stand rejected under § 112, second paragraph, as purportedly indefinite. Specifically, the Office Action asserts that the skilled artisan would not know what is meant by the alternative method steps recited in the claims. For example, the Examiner asserts that the use of "and/or" is unclear and that the recitation of alternative methods in claims 1 and 4 is also unclear. Claims 1, 4, 5, 7, 9, 11 and 12 purportedly recited alternative language such as "and/or". These claims have been amended to remove all language which recited alternative method steps. For example, claim 1 as filed recited

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both a dispersion step and an alternative emulsification step. Claim 1, as amended, recites only the dispersion step. New claim 24 recites the emulsification step.

In addition, claims reciting "and/or" have been amended to recite "and". Thus, claims 1 and 4 have been amended to recite a single step "b" rather than alternative steps "b₁" and "b₂". Claim 7 has been amended to remove the phrase "or slightly insoluble". The alternative method steps deleted from the claims have been submitted in new claims 23-44. Accordingly, the rejection under 35 U.S.C. § 112, second paragraph respectfully should be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-22 stand rejected under § 112, first paragraph, as purportedly containing subject matter which lacks adequate written description. According to the Examiner, the specification does not provide enough explanation so that the skilled artisan would be able to choose between "b₁" or "b₂" as recited in claim 1. As discussed above, claims 1 and 4 have been amended to recite a single step "b" rather than alternative steps "b₁" and "b₂". Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tice *et al.* in view of Ekman *et al.* Tice *et al.* is cited for purportedly disclosing a method of microencapsulating an agent by dissolving a polymer in a solvent and then adding an active

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ingredient. Ekman *et al.* is cited for purportedly disclosing the removal of water from a dissolved substance through the use of polyethylene glycol (PEG).

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

[W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.* . . . 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaack, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the cited art of Tice *et al.* and Ekman *et al.*, alone or in combination, do not suggest the methods claimed, let alone suggest that the claimed methods could be conducted with a reasonable expectation of success.

The present invention relates to methods of encapsulating an active substance where the polymer is initially dissolved in an organic solvent. The finding of the present invention that it is possible to use an aqueous solution of PEG as a continuous phase and as an extraction medium when making microparticles from polymers that can be dissolved in organic solvents is surprising and unexpected. The present invention also confers the new

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advantages of the reduction in the volume of organic solvents used, reduction in the energy of mixing used and avoidance of PVA and other surfactants.

The Examiner asserts that Tice *et al.* relate to a method of microencapsulating an agent to form a microencapsulated product. As disclosed in Tice *et al.*, a polymer is disclosed in a solvent, the active substance is added to the solvent and the resulting solvent mixture dispersion is added to a continuous medium to form microdroplets. However, as the Office Action states on page 4, Tice *et al.* does not disclose the use of PEG as the continuous process medium.

Further, Ekman *et al.* does not remedy the deficiencies of Tice *et al.* The Office Action reaches the following conclusion about the disclosure of Ekman *et al.*: "the method of encapsulating an active substance is whereby a biodegradable polymer is dissolved in an organic solvent, an active substance is dissolved in water or an organic solvent, and the two dispersions are mixed and added to polyethylene glycol as a continuous phase would have been known to one of ordinary skill in the art. Motivation to utilize polyethylene glycol as the continuous phase is taught by Ekman *et al.*" See Office Action, page 5. Applicants respectfully submit that this conclusion is incorrect, for the reasons set forth below.

Ekman *et al.* does not motivate the skilled artisan to use PEG as the continuous phase of the invention disclosed in Tice *et al.* Ekman *et al.* does not disclose or even suggest that microparticles could be made from polymers that are soluble in organic solvents. Rather, Ekman *et al.* focuses entirely on the preparation of microparticles made from polymers which can be dissolved in water using a two phase aqueous system. Ekman *et al.* discloses in detail methods of removing water from the inner, discontinuous, phase to form microparticles. The removal of the water is accomplished by the addition of substances, such as PEG, to the outer

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phase. The removal of the water from the inner phase containing the solidifies the water-soluble polymer that forms the microparticle matrix.

The application of the above teachings of Ekman *et al.* to the teachings of Tice *et al.* would not successfully result in the claimed invention. Ekman *et al.* discloses the removal of water. The removal of water in order to solidify a polymer which was dissolved in organic solvents, as with Tice *et al.* and the present invention, would not result in the claimed invention. In fact, removing water in the attempt to solidify a polymer dissolved in an organic solvent would be unsuccessful. Thus, the skilled artisan would not be motivated to apply the teachings of Ekman *et al.* to Tice *et al.* to reach the claimed invention because it would not result in a working invention. A reference must be considered for all it teaches alone and in combination with other references. Thus, a reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention: Panduit Corp. v. Dennison Manufacturing Co., 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir. 1987). It is impermissible with the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. In re Hedges, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986). Yet, that is exactly how the art is combined in the Office Action. The Office Action is citing parts of Ekman *et al.* which disclose the use of PEG, without analyzing the entire reference, which in practice would not remedy the deficiencies of Tice *et al.*, because combining the two cited references in their entirety would produce a method which does not work.

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Thus, the references, when considered alone or in combination do not render obvious the invention as claimed. Accordingly, Applicants respectfully request the appropriate withdrawal of the rejection.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Amendment and Reply
Marked-up Claims 1, 4, 5, 7, 9, 11 and 12

1. (Once Amended) A method of encapsulating an active substance in a biodegradable polymer, which comprises:
 - a) dissolving said biodegradable polymer in an organic solvent therefor;
 - b)[b₁)] dispersing said active substance in the organic solution obtained in step a), to provide a dispersion with the active substance as the inner phase thereof; [or alternatively
 - b₂) emulsifying said active substance, dissolved in water or other aqueous solvent therefor, in the organic solution obtained in step a), to provide an emulsion with the active substance as the inner aqueous phase thereof;] and
 - c) subjecting the dispersion obtained in step (b),[b₁), or alternatively the emulsion obtained in step b₂),] to an encapsulation operation with an aqueous polyethylene glycol solution as a continuous phase, such that micro- or nanoparticles having the active substance encapsulated therein are obtained.

4. (Twice Amended) A method according to claim 1, wherein the encapsulation operation in step c) is performed by adding the dispersion obtained in step b) [b₁), or alternatively the emulsion obtained in step b₂)], to said aqueous polyethylene glycol solution while subjection last-mentioned aqueous solution to a stirring and [and/or] homogenization operation.

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5. (Once Amended) A method according to claim 4, wherein the stirring and [and/or] homogenization operation is performed by a low intensity and [and/or] low energy process, e.g., propeller mixing or the use of motionless mixers.
7. (Twice Amended) A method according to claim 1, wherein said biodegradable polymer is insoluble[, or slightly soluble,] in the aqueous polyethylene glycol solution used in step c), preferably an aliphatic polyester.
9. (Twice Amended) A method according to claim 1, wherein said biodegradable polymer is selected from homo or copolymers prepared from α -hydroxy acids, preferably lactic acid and glycolic acid, and [and/or] cyclic dimers of α -hydroxy acids, preferably lactides and glycolides.
11. (Twice Amended) A method according to claim 1, wherein said organic solvent used in step a) is immiscible or essentially immiscible with said aqueous polyethylene glycol solution used in step c), but slightly or very slightly soluble therein, and capable of dissolving said biodegradable polymer, and is preferably selected from ethyl acetate, dichloromethane, methyl ethyl ketone and [and/or] methyl isobutyl ketone.
12. (Twice Amended) A method according to claim 1, wherein the active substance which is dispersed in step b) [b₁)] has a particle size within the range of about 0.5-20 μm , preferably 0.5-10 μm , more preferably 0.5-3 μm .